

## WHAT IS CLAIMED IS:

1. A method for identifying a drug lead compound that binds to a target biological molecule (TBM) of interest, the method comprising:

(a) assembling a library of candidate target binding fragments (CTBF) capable of being chemically cross-linked by a cross-linker to provide candidate cross-linked target binding fragments for binding to the target biological molecule;

(b) screening the library of candidate target binding fragments to identify at least first and second candidate target binding fragments that bind to the target biological molecule;

(c) chemically cross-linking the at least first and second candidate target binding fragments or structurally related analogs thereof with a cross-linker to provide a library of candidate cross-linked target binding fragments for binding to the target biological molecule; and

(d) screening the library obtained in (c) to identify a drug lead compound that binds to the target biological molecule.

2. The method according to Claim 1, wherein at least one of the candidate target binding fragments of the library of candidate target binding fragments binds to the target biological molecule with a  $K_d$  of from about 5 mM to about 0.05 mM.

3. The method according to Claim 1, wherein at least one of the candidate target binding fragments of the library of candidate target binding fragments binds to the target biological molecule with a  $K_d$  of from about 3 mM to about 0.1 mM.

4. The method according to Claim 1, wherein the drug lead compound identified in step (d) binds to the target biological molecule with a  $K_d$  of 500 nM or lower.

5. The method according to Claim 1, wherein the screening steps (b) and (c) consist essentially of an *in vitro* biological assay.

6. The method according to Claim 1, wherein the library of candidate cross-linked target binding fragments for binding to the target biological molecule comprises homodimeric or heterodimeric candidate cross-linked target binding fragments.

7. The method according to Claim 1, wherein the library of candidate target binding fragments comprises candidate target binding fragments of less than about 500 daltons.

8. The method according to Claim 1 wherein the library of candidate cross-linked target binding fragments comprises candidate cross-linked target binding fragments of less than about 750 daltons.

9. The method according to Claim 1, wherein the target biological molecule is a human or human pathogen protein.

10. The method according to Claim 9, wherein the protein is an enzyme, a human hormone, a human receptor and fragments thereof having nitrogen's in the protein present in their naturally occurring isotopic abundance.

11. The method according to Claim 1, wherein at least one of the screening steps (b) and (d) is accomplished by ELISA assay.

12. A method for inhibiting the binding of a first biological molecule to a second biological molecule that binds to the first biological molecule, the method comprising:

contacting a system comprising both the first and second biological molecules with a binding inhibitory amount of a drug lead compound identified according to the method of Claim 1, wherein the drug lead compound binds to the first biological molecule and inhibits its ability to bind to the second biological molecule.

13. The method according to Claim 12, wherein the first and second biological molecules are human proteins.

14. The method according to Claim 13, wherein the first and second biological molecules are selected from the group; a human hormone, cytokine or chemokine, a human receptor and fragments thereof

15. A method for identifying a drug lead compound that binds to a target biological molecule of interest, the method comprising:

- 10 (a) assembling a library of candidate target binding fragments, each fragment containing an oxime linking group;
- (b) screening the library of candidate target binding fragments or monomers to identify at least first and second oxime containing candidate target binding fragments that bind to the target biological molecule;
- 15 (c) chemically crosslinking the aldehyde analogs of the at least first and second oxime containing candidate target binding fragments with an O,O'-diamino-alkanediol cross-linker to provide a library of oxime containing candidate cross-linked target binding fragments for binding to the target biological molecule; and
- (d) screening the library obtained in (c) to identify a drug lead compound
- 20 that binds to the target biological molecule.

16. A method comprising:

- (a) assembling a library of candidate target binding fragments (CTBF), each fragment having a linkable functional group (LFG) or blocked form thereof (BLFG), the blocked form containing a linking group (LG);
- 25 (b) contacting the candidate target binding fragments with a target biological molecule (TBM);
- (c) measuring a change in a first physical association (PA-1) of the target biological molecule;
- 30 (d) selecting target binding fragments (TBF) based on (c);
- (e) reacting selected target binding fragments having a linkable functional group with a cross-linker, having chemically compatible cross-reactive groups (CFG)

with the LFG, under conditions suitable for forming a library of candidate cross-linked target binding fragments (CXL-TBF);

(f) contacting the candidate cross-linked target binding fragments with the target biological molecule (TBM);

5 (g) measuring a change in a second physical association (PA-2) of the target biological molecule;

(h) selecting cross-linked target binding fragments (XL-TBF) based on (g).

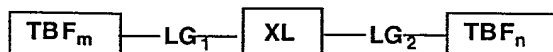
10 17. The method of Claim 16 wherein the candidate target binding fragment contacted with the TBM contains a blocked linkage functional group (BLFG) containing linking group LG.

15 18. The method of Claim 17 where in the linking group (LG) in BLFG is selected from the group; oxime, hydrazone, N-acyl hydrazone, secondary amine, tertiary amine, acetal, ketal, 1,2 amino alcohols, amide, N,N-disubstituted amides, thioamide, ureido, thioureido, carbamate, thiocarbamate, thiothiocarbamate, sulfonamide, carbonate, guanidino, amidino, thioester, ester, ether, 2-hydroxyether, 2-hydroxythioether, thioether, disulfide, alkane (alkylene), alkene (alkenylene) and alkyne (alkynylene).

20 19. The method of Claim 18 wherein each candidate target binding fragment (CTBF) of step (b) contains the same linking group (LG) as is present in the candidate cross-linked target binding fragment (CXL-TBF) of step (f).

25 20. The method of Claim 19 wherein the linking group (LG) is selected from the group; oxime, secondary amine, tertiary amine, amide, ureido, thioureido, sulfonamide and carbamate.

30 21. The method of Claim 19 wherein two candidate target binding fragments (CTBF) selected from step (d) are cross-linked to form a candidate cross-linked target binding fragment (CXL-TBF) represented by



where

5  $\text{TBF}_m$  is a first TBF selected from step (d) which contained  $\text{LG}_1$  in its blocked linking group ;

$\text{TBF}_n$  is a second TBF selected from step (d) which contained  $\text{LG}_2$  in its blocked linking group;

$\text{XL}$  represents the cross-linker without the chemically compatible cross-reactive functional groups;

10  $\text{LG}_1$  represents the linking group in the first TBF; and

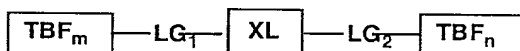
$\text{LG}_2$  represents the linking group in the second TBF.

22. The method of Claim 21 wherein  $\text{LG}_1$  and  $\text{LG}_2$  are the same or are different and are selected from the group oxime, secondary amine, tertiary amine, amide, ureido, thioureido, sulfonamide and carbamate.

23. The method of Claim 21 wherein  $\text{TBF}_m$  and  $\text{TBF}_n$  are the same or are different.

20 23. The method of Claim 21 where  $\text{XL}$  is selected from the group of alkanes: methylene, ethylene, propylene, butylene, pentylene, hexylene and heptylene, optionally containing 0, 1, 2 or 3 ether linkages and from 1-3 double bonds and aryls: ortho-, meta- or para-  $\text{C}_0\text{-C}_6\text{-alkyl-phenyl-C}_0\text{-C}_6\text{-alkylene}$ .

25 24. The method of Claim 16 wherein the candidate cross-linked target binding fragments are represented by the formula:



30 where

$\text{TBF}_m$  represents a first TBF selected from step (d);

$\text{TBF}_n$  represents a second TBF selected from step (d);

XL represents the cross-linker without the chemically compatible cross-reactive functional groups selected from the group

$C_0$ - $C_{10}$ -alkylene,  
 $C_0$ - $C_6$ -alkyl- $C_6$ - $C_{10}$ -aryl- $C_0$ - $C_6$ -alkylene,  
 $C_1$ - $C_6$ -alkyl- $N(R_1)$ - $C_1$ - $C_6$ -alkylene,  
 $(C_1$ - $C_6$ -alkyl-O- $C_1$ - $C_6$ -alkylene) $_n$ , where  $n=1, 2, 3$  or  $4$ ;

$LG_1$  and  $LG_2$  are linking groups independently selected from the group

- $C(R_a)=N-O$ -, - $O-N=C(R_a)$ -, - $CH_2-N(R_a)$ -, - $N(R_a)-CH_2$ -,  
- $C(=O)-N(R_a)$ -, - $N(R_a)-C(=O)$ -, - $N(R_a)-C(=O)-O$ -, - $O-C(=O)-N(R_a)$ -,  
- $N(R_a)-C(=O)-N(R_b)$ -, - $N(R_a)-C(=O)-N(R_b)$ -, - $SO_2-N(R_a)$ - and  
- $N(R_a)-SO_2$ -;

$R_a$  and  $R_b$  are independently selected from the group

hydrogen,  $C_1$ - $C_{10}$ -alkyl,  $C_0$ - $C_{10}$ -alkyl- $C_6$ - $C_{10}$ -aryl,  $C_6$ - $C_{10}$ -aryl- $C_0$ - $C_{10}$ -alkyl,  $C_0$ - $C_{10}$ -alkyl-heterocycle- $C_0$ - $C_{10}$ -alkyl,  $C_1$ - $C_6$ -alkyl-NH- $C_1$ - $C_6$ -alkyl,  $C_0$ - $C_{10}$ -alkyl-O- $C_0$ - $C_{10}$ -alkyl,  $C_0$ - $C_{10}$ -alkyl-C(=O)- $C_0$ - $C_{10}$ -alkyl,  $C_0$ - $C_{10}$ -alkyl-NH-C(=O)- $C_0$ - $C_{10}$ -alkyl,  $C_0$ - $C_{10}$ -alkyl-O-C(=O)- $C_0$ - $C_{10}$ -alkyl, where any alkyl, aryl or heterocycle is optionally substituted with  $C_1$ - $C_{10}$ -alkyl,  $C_1$ - $C_{10}$ -alkoxy,  $C_6$ - $C_{10}$ -aryl,  $C_6$ - $C_{10}$ -aryloxy, halo (F, Cl, Br, I), hydroxy, carboxy, amino, nitro and  $S(O)_{0.3}$ .

25. The method of Claim 24 wherein the  $TBF_m$  and  $TBF_n$  from step (d) each independently bind to the target biological molecule with a  $K_d$  of from about 3 mM to about 100  $\mu$ M.

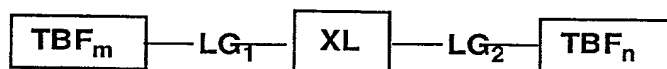
26. The method of Claim 25 wherein the  $TBF_m$  and  $TBF_n$  from step (d) each independently bind to the target biological molecule with a  $K_d$  of from about 2 mM to about 500  $\mu$ M.

27. The method according to Claim 24, wherein the target biological molecule is a human or human pathogen protein.

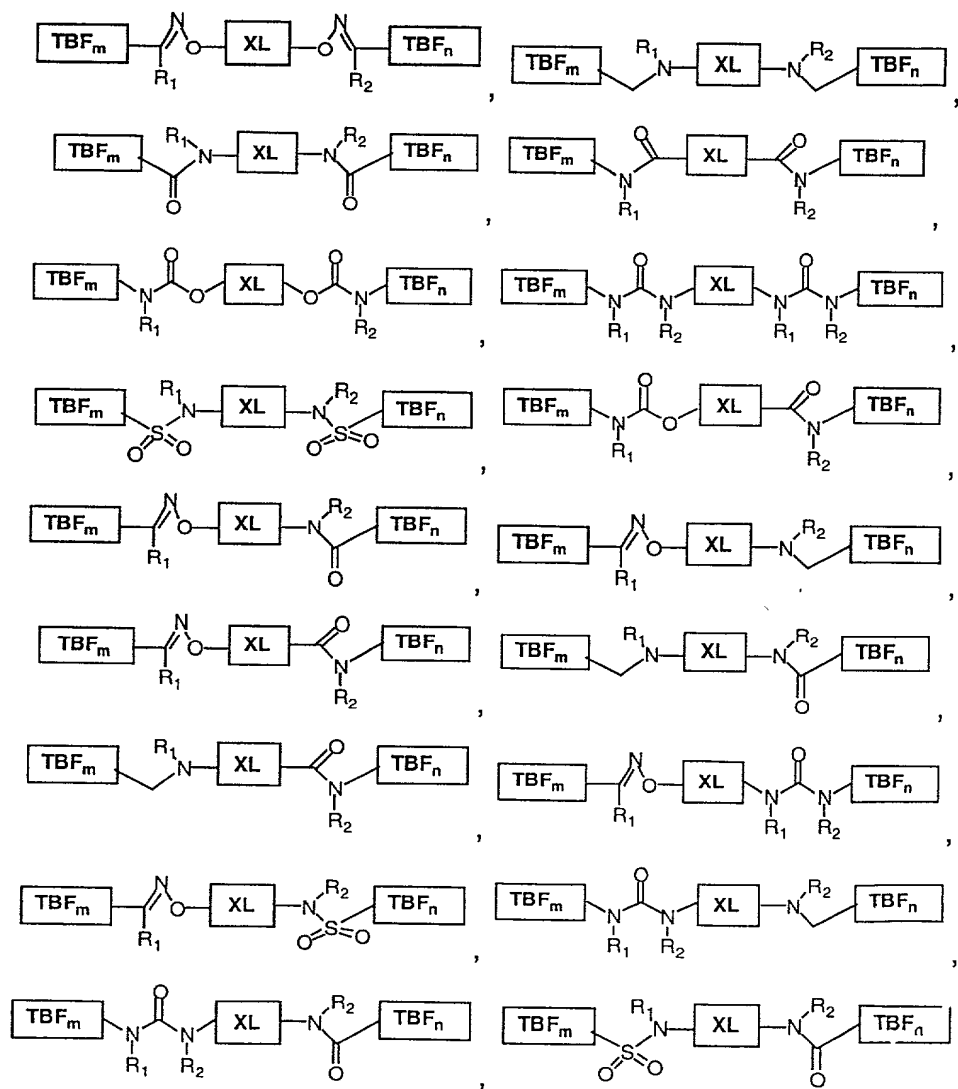
28. The method according to Claim 24, wherein the protein is an enzyme, a human hormone or a human receptor having nitrogen's in their naturally occurring isotopic abundance.

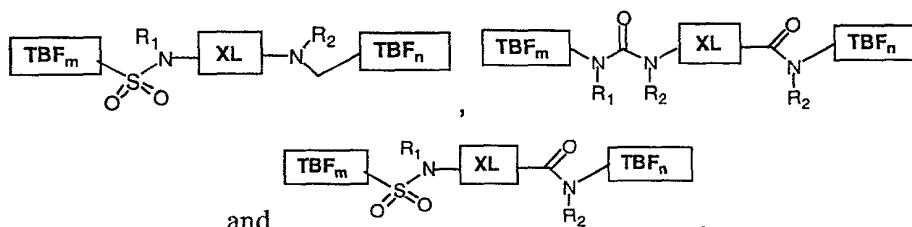
29. The method according to Claim 24, wherein at least one of steps (b) and (d) is accomplished by ELISA assay.

30. The method of Claim 21 wherein



is selected from the group;

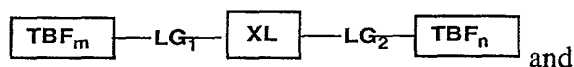




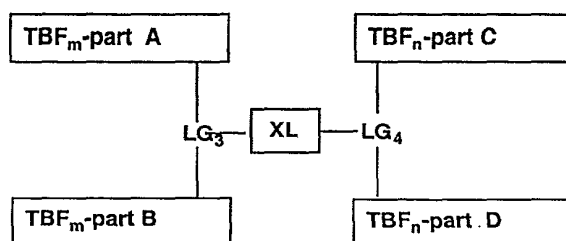
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31. The method of Claim 16 wherein the candidate cross-linked target binding fragments are represented by the formulae:

10



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where

TBF<sub>m</sub> represents a first TBF selected from step (d);

TBF<sub>n</sub> represents a second TBF selected from step (d);

20

TBF<sub>m</sub>-part A and B represent TBF<sub>m</sub> from step (d) where each fragment is bonded to a single atom in LG<sub>3</sub>;

TBF<sub>n</sub>-part C and D represent TBF<sub>n</sub> from step (d) where each fragment is bonded to a single atom in LG<sub>4</sub>;

XL represents a cross-linker of the formula

25

-(C<sub>0</sub>-C<sub>2</sub>-alkyl-L<sup>1</sup>-L<sup>2</sup>-L<sup>3</sup>-L<sup>4</sup>-L<sup>5</sup>-C<sub>0</sub>-C<sub>2</sub>-alkyl)-;

LG<sub>1</sub> and LG<sub>2</sub> are linking groups independently selected from the group

-C(R<sub>a</sub>)=N-O-, -O-N=C(R<sub>a</sub>)-, -CH<sub>2</sub>-N(R<sub>a</sub>)-, -N(R<sub>a</sub>)-CH<sub>2</sub>-, -C(=O)-N(R<sub>a</sub>)-, -N(R<sub>a</sub>)-C(=O)-, -N(R<sub>a</sub>)-C(=O)-O-, -O-C(=O)-N(R<sub>a</sub>)-, -N(R<sub>a</sub>)-C(=O)-N(R<sub>b</sub>)-, -N(R<sub>a</sub>)-C(=O)-N(R<sub>b</sub>)-, -SO<sub>2</sub>-N(R<sub>a</sub>)- and -N(R<sub>a</sub>)-SO<sub>2</sub>-;

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LG<sub>3</sub> and LG<sub>4</sub> are linking groups independently selected from the group

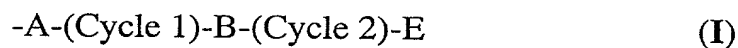
>C=N-O-, -O-N=C<, -CH<sub>2</sub>-N<, >N-CH<sub>2</sub>-, -C(=O)-N<, >N-C(=O)-, >N-C(=O)-O-, -O-C(=O)-N<, >N-C(=O)-N(R<sub>b</sub>)-, -N(R<sub>a</sub>)-C(=O)-N<, -SO<sub>2</sub>-N< and >N-SO<sub>2</sub>-, where < and



> represent two bonds linking TBF-part A, B, C, or D to the single N or C atom in LG<sub>3</sub> or LG<sub>4</sub>;

R<sub>a</sub> and R<sub>b</sub> are independently selected from the group  
hydrogen, C<sub>1</sub>-C<sub>10</sub>-alkyl, C<sub>0</sub>-C<sub>10</sub>-alkyl-C<sub>6</sub>-C<sub>10</sub>-aryl, C<sub>6</sub>-C<sub>10</sub>-aryl-C<sub>0</sub>-C<sub>10</sub>-alkyl, C<sub>0</sub>-C<sub>10</sub>-alkyl-  
5 heterocycle-C<sub>0</sub>-C<sub>10</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkyl-NH-C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>0</sub>-C<sub>10</sub>-alkyl-O-C<sub>0</sub>-C<sub>10</sub>-alkyl, C<sub>0</sub>-  
C<sub>10</sub>alkyl-C(=O)-C<sub>0</sub>-C<sub>10</sub>-alkyl, C<sub>0</sub>-C<sub>10</sub>-alkyl-NH-C(=O)-C<sub>0</sub>-C<sub>10</sub>-alkyl, C<sub>0</sub>-C<sub>10</sub>-alkyl-O-  
C(=O)-C<sub>0</sub>-C<sub>10</sub>-alkyl, where any alkyl, aryl or heterocycle is optionally substituted  
with C<sub>1</sub>-C<sub>10</sub>-alkyl, C<sub>1</sub>-C<sub>10</sub>-alkoxy, C<sub>6</sub>-C<sub>10</sub>-aryl, C<sub>6</sub>-C<sub>10</sub>-aryloxy, halo (F, Cl, Br, I),  
hydroxy, carboxy, amino, nitro and S(O)<sub>0.3</sub>;

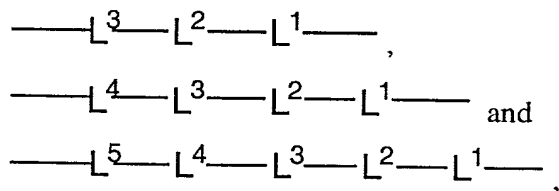
10 TBF<sub>m</sub>, TBF<sub>n</sub>, TBF<sub>m</sub>-part A, TBF<sub>m</sub>-part B, TBF<sub>n</sub>-part C and TBF<sub>n</sub>-part D are  
each independently represented by formula I



15 Where

Cycle 1 and Cycle 2 are independently present or absent and are selected from  
a mono-, bi-, or tricyclic saturated, unsaturated, or aromatic ring, each ring having 5,  
6 or 7 atoms in the ring where the ring atoms are carbon or from 1-4 heteroatoms  
selected from; nitrogen, oxygen, and sulfur, and where any sulfur ring atom may  
20 optionally be oxidized and any carbon ring atom may form a double bond with O, NR<sup>n</sup>  
and CR<sup>1</sup>R<sup>1'</sup>, each ring nitrogen may be substituted with R<sup>n</sup> and any ring carbon may  
be substituted with R<sup>d</sup>;

25 A and B are independently selected from



30 where:

L<sup>1</sup> is absent or may be selected from oxo (O), S(O)<sub>5</sub>, C(=O), C(=N-R<sup>n</sup>),  
C(=CR<sup>1</sup>R<sup>1'</sup>), C(R<sup>1</sup>R<sup>1'</sup>), C(R<sup>1</sup>), C, het, N(R<sup>n</sup>) or N;

$L^2$  is absent or may be selected from oxo (O),  $S(O)_s$ ,  $C(=O)$ ,  $C(=N-R^n)$ ,  
 $C(=CR^2R^{2'})$ ,  $C(R^2R^{2'})$ ,  $C(R^2)$ , C, het,  $N(R^n)$  or N;

$L^3$  is absent or may be selected from oxo (O),  $S(O)_s$ ,  $C(=O)$ ,  $C(=N-R^n)$ ,  
5  $C(=CR^3R^{3'})$ ,  $C(R^3R^{3'})$ ,  $C(R^3)$ , C, het,  $N(R^n)$  or N;

$L^4$  is absent or may be selected from oxo (O),  $S(O)_s$ ,  $C(=O)$ ,  $C(=N-R^n)$ ,  
 $C(=CR^4R^{4'})$ ,  $C(R^4R^{4'})$ ,  $C(R^4)$ , C,  $NR^n$  or N; and

10  $L^5$  is absent or may be selected from oxo (O),  $S(O)_s$ ,  $C(=O)$ ,  $C(=N-R^n)$ ,  
 $C(R^5R^{5'})$ ,  $C(=CR^5R^{5'})$ ,  $C(R^5)$ , C,  $NR^n$  or N;

$R^1$ ,  $R^{1'}$ ,  $R^2$ ,  $R^{2'}$ ,  $R^3$ ,  $R^{3'}$ ,  $R^4$ ,  $R^{4'}$ ,  $R^5$  and  $R^{5'}$  each are independently  
selected from  $R^a$ ,  $R^{a'}$ ,  $R^c$  and U-Q-V-W; where s is 0-2

15 Optionally, each  $R^1-R^5$  or  $NR^n$  together with any other  $R^1-R^5$  or  $NR^n$  may  
form a mono-, bi-, or tricyclic saturated, unsaturated, or aromatic ring, each ring being  
a homo- or heterocycle having 5, 6 or 7 atoms in the ring, optionally each ring  
containing 1-4 heteroatoms selected from N, O and S where any ring carbon or sulfur  
atom may optionally be oxidized, each ring nitrogen optionally substituted with  $R^n$   
20 and each ring carbon optionally substituted with  $R^d$ ;

E is  $-L^1-L^2-L^3-R^a$ ;

25  $R^a$  is selected from the group; hydrogen, halo(F, Cl, Br, I), halo(F, Cl, Br, I)-  
 $C_1-C_{11}$  alkyl, halo(F, Cl, Br, I)- $C_1-C_{11}$  alkoxy, hydroxy- $C_1-C_{11}$  alkyl, cyano,  
isocyanate, carboxy- $C_1-C_{11}$  alkyl, amino,  $C_0-C_{11}$  alkyl-amino- $(C_1-C_8$  alkyl),  $C_0$ -  
 $C_{11}$  alkyl-amino-di- $(C_1-C_8$  alkyl), aminocarbonyl,  $C_1-C_{11}$  alkylcarbonylamino,  
carboxamido, carbamoyl, carbamoyloxy, formyl, formyloxy, azido, nitro, hydrazide,  
30 hydroxamic acid, imidazolyl, ureido, thioureido, thiocyanato, hydroxy,  $C_1-C_6$  alkoxy,  
mercapto, sulfonamido, het, phenoxy, phenyl, benzyl, benzyloxy, benzamido, tosyl,  
morpholino, morpholinyl, piperazinyl, piperidinyl, pyrrolinyl, imidazolyl and indolyl;

$R^{a'}$  is selected from the group of  $C_0-C_{10}$ alkyl-Q- $C_0-C_6$ alkyl,  $C_0-C_{10}$ alkenyl-Q- $C_0-C_6$ alkyl,  $C_0-C_{10}$ alkynyl-Q- $C_0-C_6$ alkyl,  $C_3-C_{11}$ cycloalkyl-Q- $C_0-C_6$ alkyl,  $C_3-C_{10}$ cycloalkenyl-Q- $C_0-C_6$ alkyl,  $C_1-C_6$ alkyl- $C_6-C_{12}$ aryl-Q- $C_0-C_6$ alkyl,  $C_6-C_{10}$ aryl- $C_1-C_6$ alkyl-Q- $C_0-C_6$ alkyl,  $C_0-C_6$ alkyl-het-Q- $C_0-C_6$ alkyl,  $C_0-C_6$ alkyl-Q-het- $C_0-C_6$ alkyl, het- $C_0-C_6$ alkyl-Q- $C_0-C_6$ alkyl,  $C_0-C_6$ alkyl-Q- $C_6-C_{12}$ aryl and Q- $C_1-C_6$ alkyl, where any aryl or het is optionally substituted with 1-3  $R^d$  and any alkyl, alkenyl or alkynyl is optionally substituted with 1-3  $R^a$ ;

$R^a$  and  $R^{a'}$  may join to form a 3-7 member homocyclic ring substituted with 1-3  $R^a$ ;

$R^c$  is selected from hydrogen and substituted or unsubstituted; amino, O- $C_1-C_8$ alkyl, amino-( $C_1-C_8$ alkyl), amino-di-( $C_1-C_8$ alkyl),  $C_1-C_{10}$ alkyl,  $C_2-C_{10}$ alkenyl,  $C_2-C_{10}$ alkynyl,  $C_3-C_{11}$ cycloalkyl,  $C_3-C_{10}$ cycloalkenyl,  $C_1-C_6$ alkyl- $C_6-C_{12}$ aryl,  $C_6-C_{10}$ aryl- $C_1-C_6$ alkyl,  $C_1-C_6$ alkyl-het, het- $C_1-C_6$ alkyl,  $C_6-C_{12}$ aryl and het, where the substituents on any alkyl, alkenyl or alkynyl are 1-3  $R^a$  and the substituents on any aryl or het are 1-3  $R^d$ ;

$R^d$  is selected from  $R^h$  and  $R^p$ ;

$R^h$  is selected from the group OH,  $OCF_3$ ,  $OR^c$ ,  $SR^m$ , halo(F, Cl, Br, I), CN, isocyanate,  $NO_2$ ,  $CF_3$ ,  $C_0-C_6$ alkyl- $NR^nR^{n'}$ ,  $C_0-C_6$ alkyl-C(=O)- $NR^nR^{n'}$ ,  $C_0-C_6$ alkyl-C(=O)- $R^a$ ,  $C_1-C_8$ alkyl,  $C_1-C_8$ alkoxy,  $C_2-C_8$ alkenyl,  $C_2-C_8$ alkynyl,  $C_3-C_6$ cycloalkyl,  $C_3-C_6$ cycloalkenyl,  $C_1-C_6$ alkyl-phenyl, phenyl- $C_1-C_6$ alkyl,  $C_1-C_6$ alkyloxycarbonyl, phenyl- $C_0-C_6$ alkyloxy,  $C_1-C_6$ alkyl-het, het- $C_1-C_6$ alkyl,  $SO_2$ -het, O- $C_6-C_{12}$ aryl,  $SO_2-C_6-C_{12}$ aryl,  $SO_2-C_1-C_6$ alkyl and het, where any alkyl, alkenyl or alkynyl may optionally be substituted with 1-3 groups selected from OH, halo(F, Cl, Br, I), nitro, amino and aminocarbonyl, where the substituents on any aryl

or het are 1-2 hydroxy, halo(F, Cl, Br, I),  $\text{CF}_3$ ,  $\text{C}_1\text{-C}_6$ alkyl,  $\text{C}_1\text{-C}_6$ alkoxy, nitro and amino;

$\text{R}^m$  is selected from hydrogen,  $\text{S-C}_1\text{-C}_6$ alkyl,  $\text{C(=O)-C}_1\text{-C}_6$ alkyl,  $\text{C(=O)-NR}^n\text{R}^{n'}$ ,  $\text{C}_1\text{-C}_6$ alkyl, halo(F, Cl, Br, I)- $\text{C}_1\text{-C}_6$ alkyl, benzyl and phenyl;

$\text{R}^n$  is selected from the group  $\text{R}^c$ , OH,  $\text{OCF}_3$ ,  $\text{OR}^o$ , CN, isocyanate,  $\text{NH-C(=O)-O-R}^c$ ,  $\text{NH-C(=O)-R}^c$ ,  $\text{NH-C(=O)-NHR}^c$ ,  $\text{NH-SO}_2\text{-R}^s$ ,  $\text{NH-SO}_2\text{-NH-C(=O)-R}^c$ ,  $\text{NH-C(=O)-NH-SO}_2\text{-R}^s$ ,  $\text{C(=O)-O-R}^o$ ,  $\text{C(=O)-R}^c$ ,  $\text{C(=O)-NHR}^c$ ,  $\text{C(=O)-NH-C(=O)-O-R}^o$ ,  $\text{C(=O)-NH-C(=O)-R}^c$ ,  $\text{C(=O)-NH-SO}_2\text{-R}^s$ ,  $\text{C(=O)-NH-SO}_2\text{-NHR}^c$ ,  $\text{SO}_2\text{-R}^s$ ,  $\text{SO}_2\text{-O-R}^o$ ,  $\text{SO}_2\text{-N(R}^c)_2$ ,  $\text{SO}_2\text{-NH-C(=O)-O-R}^o$ ,  $\text{SO}_2\text{-NH-C(=O)-O-R}^o$  and  $\text{SO}_2\text{-NH-C(=O)-R}^c$ ;

$\text{R}^o$  is selected from hydrogen and substituted or unsubstituted  $\text{C}_1\text{-C}_6$ alkyl,  $\text{C}_0\text{-C}_6$ alkyl- $\text{C}_6\text{-C}_{10}$ aryl,  $\text{C}_1\text{-C}_6$ alkylcarbonyl,  $\text{C}_2\text{-C}_6$ alkenyl,  $\text{C}_2\text{-C}_6$ alkynyl,  $\text{C}_3\text{-C}_8$ cycloalkyl and benzoyl, where the substituents on any alkyl are 1-3  $\text{R}^a$  and the substituents on any aryl are 1-3  $\text{R}^p$ ;

$\text{R}^p$  is selected from the group; OH, halo(F, Cl, Br, I), CN, isocyanate,  $\text{OR}^o$ ,  $\text{SR}^m$ ,  $\text{SOR}^o$ ,  $\text{NO}_2$ ,  $\text{CF}_3$ ,  $\text{R}^c$ ,  $\text{NR}^n\text{R}^{n'}$ ,  $\text{N(R}^n\text{)-C(=O)-O-R}^o$ ,  $\text{N(R}^n\text{)-C(=O)-R}^c$ ,  $\text{C}_0\text{-C}_6$ alkyl- $\text{SO}_2\text{-R}^s$ ,  $\text{C}_0\text{-C}_6$ alkyl- $\text{SO}_2\text{-NR}^n\text{R}^{n'}$ ,  $\text{C(=O)-R}^c$ ,  $\text{O-C(=O)-R}^c$ ,  $\text{C(=O)-O-R}^o$  and  $\text{C(=O)-NR}^n\text{R}^{n'}$ , where the substituents on any alkyl, alkenyl or alkynyl are 1-3  $\text{R}^a$  and the substituents on any aryl or het are 1-3  $\text{R}^d$ ;

$\text{R}^s$  is a substituted or unsubstituted group selected from;  $\text{C}_1\text{-C}_8$ alkyl,  $\text{C}_2\text{-C}_8$ alkenyl,  $\text{C}_2\text{-C}_8$ alkynyl,  $\text{C}_3\text{-C}_8$ cycloalkyl,  $\text{C}_3\text{-C}_6$ cycloalkenyl,  $\text{C}_0\text{-C}_6$ alkyl-phenyl, phenyl- $\text{C}_0\text{-C}_6$ alkyl,  $\text{C}_0\text{-C}_6$ alkyl-het and het- $\text{C}_0\text{-C}_6$ alkyl, where the substituents on any

alkyl, alkenyl or alkynyl are 1-3 R<sup>a</sup> and the substituents on any aryl or het are 1-3 R<sup>d</sup>;

het is any mono-, bi-, or tricyclic saturated, unsaturated, or aromatic ring where at least one ring is a 5-, 6- or 7-membered ring containing from one to four heteroatoms selected from the group nitrogen, oxygen, and sulfur, the 5-membered  
5 ring having from 0 to 2 double bonds and the 6- or 7-membered ring having from 0 to 3 double bonds and where any carbon or sulfur atoms in the ring may optionally be oxidized, and where any nitrogen heteroatom may optionally be quaternized and where any ring may contain from 0-3 R<sup>d</sup>;

10 U is an optionally substituted bivalent radical selected from the group; C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>0</sub>-C<sub>6</sub>alkyl-Q, C<sub>2</sub>-C<sub>6</sub>alkenyl-Q, and C<sub>2</sub>-C<sub>6</sub>alkynyl-Q, where the substituents on any alkyl, alkenyl or alkynyl are 1-3 R<sup>a</sup>;

15 Q is absent or is selected from the group; -O-, -S(O)<sub>s</sub>-, -SO<sub>2</sub>-N(R<sup>n</sup>)-, -N(R<sup>n</sup>)-, -N(R<sup>n</sup>)-C(=O)-, -N(R<sup>n</sup>)-C(=O)-O-, -N(R<sup>n</sup>)-SO<sub>2</sub>-, -C(=O)-, -C(=O)-O-, -het-, -C(=O)-N(R<sup>n</sup>)-, -PO(OR<sup>c</sup>)O- and -P(O)O-, where s is 0-2 and the heterocyclic rings substituted with 0-3 R<sup>h</sup>;

20 V is absent or is an optionally substituted bivalent group selected from C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>3</sub>-C<sub>8</sub>cycloalkyl, C<sub>0</sub>-C<sub>6</sub>alkyl-C<sub>6</sub>-C<sub>10</sub>aryl, and C<sub>0</sub>-C<sub>6</sub>alkyl-het, where the substituents on any alkyl are 1-3 R<sup>a</sup> and the substituents on any aryl or het are 1-3 R<sup>d</sup>;

25 W is selected from the group; hydrogen, -OR<sup>o</sup>, -SR<sup>m</sup>, -NR<sup>n</sup>R<sup>n'</sup>, -NH-C(=O)-O-R<sup>o</sup>, -NH-C(=O)-NR<sup>n</sup>R<sup>n'</sup>, -NH-C(=O)-R<sup>c</sup>, -NH-SO<sub>2</sub>-R<sup>s</sup>, -NH-SO<sub>2</sub>-NR<sup>n</sup>R<sup>n'</sup>, -NH-SO<sub>2</sub>-NH-C(=O)-R<sup>c</sup>, -NH-C(=O)-NH-SO<sub>2</sub>-R<sup>s</sup>, -C(=O)-NH-C(=O)-O-R<sup>o</sup>, -C(=O)-NH-C(=O)-R<sup>c</sup>, -C(=O)-NH-C(=O)-NR<sup>n</sup>R<sup>n'</sup>, -C(=O)-NH-SO<sub>2</sub>-R<sup>s</sup>, -C(=O)-NH-SO<sub>2</sub>-NR<sup>n</sup>R<sup>n'</sup>, -C(=S)-NR<sup>n</sup>R<sup>n'</sup>, -SO<sub>2</sub>-R<sup>s</sup>, -SO<sub>2</sub>-O-R<sup>o</sup>, -SO<sub>2</sub>-NR<sup>n</sup>R<sup>n'</sup>, -SO<sub>2</sub>-NH-C(=O)-O-R<sup>o</sup>, -SO<sub>2</sub>-NH-C(=O)-NR<sup>n</sup>R<sup>n'</sup>, -SO<sub>2</sub>-NH-C(=O)-R<sup>c</sup>, -O-C(=O)-NR<sup>n</sup>R<sup>n'</sup>, -O-C(=O)-

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$R^C$ ,  $-O-C(=O)-NH-C(=O)-R^C$ ,  $-O-C(=O)-NH-SO_2-R^S$  and  $-O-SO_2-R^S$ ;

Optionally,  $TBF_m$ -part A together with  $TBF_m$ -part B and  $TBF_n$ -part C together with  $TBF_n$ -part D may independently form (Cycle 1) substituted with -B-(Cycle 2)-E..

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**31** A compound made by the method of Claim 30.

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